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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/044,696	03/18/98	BARCHFELD G	1393.002

027476
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HM12/1024

EXAMINER	
DEVI,S	
ART UNIT	PAPER NUMBER
1645	24

DATE MAILED: 10/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/044,696	Barchfeld et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 14, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19, 21, and 23-30* is/are pending in the application.

4a) Of the above, claim(s) *1-18* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *19, 21, 23, and 25-30* is/are rejected.

7) ☒ Claim(s) *24* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s): 4, 5 & 16, (resupplied).

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 05/14/01 (paper no. 22) in response to the non-final action mailed 01/12/01 (paper no. 19), which amendment has been entered.

Status of Claims

2) No claims have been amended via the amendment filed 05/14/01.

Claims 1-19, 21 and 23-30 are pending in this application.

Claim 19, 21 and 23-30 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statements Re-supplied

5) Initialed copies of the PTO 1449 forms submitted on 07 May 1998, 11 September 1998 and 18 July 2000 are re-supplied to Applicants as attachments to the instant Office Action (paper no. 23).

Objection Maintained

6) The objection to the drawings made under 37 C.F.R 1.84 in paragraph 7 of the Office Action mailed 08/04/99 (paper no. 10) is maintained for reasons set forth therein.

7) The objection to claim 24 made in paragraph 17 of the Office Action mailed 01/12/01 (paper no. 19) is maintained for reasons set forth therein.

Rejection(s) Maintained

8) The rejection of claims 19, 21, 23 and 25-27 made in paragraph 14 of the Office Action mailed 01/12/01 (paper no. 19) under 35 U.S.C. § 102(e) as being anticipated by Domenighini *et*

al. (US 6,149,919 with an effective filing date of 12/30/1992) ('919) as evidenced by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996, already of record) or Partidos *et al.* (*Immunology* 89: 483-487, December 1996, already of record), is maintained for reasons set forth therein and herebelow.

Applicants assert that the reference of Domenighini *et al.* does not anticipate the claimed methods, because Domenighini *et al.* do not teach or suggest all elements of the claims. Applicants contend that the pending claims specify that 'their methods employ LT mutants as **parenteral** adjuvants' [Emphasis in original]. Applicants state that the pending claims are not directed to use of detoxified LT mutants as mucosal adjuvants. Applicants assert that Domenighini does not disclose or suggest methods in which LT mutants act as parenteral adjuvants. Applicants further contend that Domenighini fails to disclose that bacterial cell wall components are antigens.

Applicants' arguments have been carefully considered, but are not persuasive. The references of Siadak *et al.* (US 4,834,975), Golding (US 5,824,310) and Clements *et al.* (WO 9606627) are discussed herebelow solely for the purpose of rebutting Applicants' arguments and showing what is inherent from the teachings of Domenighini *et al.* in light of what is well known in the art of Microbiology and Immunology.

The base claim 19 is directed to a method for "immunizing" a vertebrate subject comprising 'parenterally administering' to the vertebrate subject an immunologically effective amount of an "adjuvant", LT-R72 or LT-K63, in combination with a pharmaceutically acceptable carrier and at least one selected antigen. Claim 19 is **not** directed to a method of increasing the immunogenicity of a selected antigen in a vertebrate subject comprising parenterally administering to the vertebrate subject an adjuvant effective amount of an adjuvant and a selected antigen, wherein the adjuvant enhances the immunogenicity of the selected antigen by showing a significant fold-increase. The 'adjuvant' recited in part (a) of claim 19 is **not** limited to a 'parenteral' adjuvant and therefore, encompasses a non-parenteral adjuvant. Claim 19, as drafted currently, is simply drawn to a method of immunization by parenteral administration of an art-known adjuvant product, such as, LT-K63 along with an antigen and a pharmaceutical carrier. One of ordinary skill in the art readily understands that when one administers an art-known

adjuvant along with a selected art-known antigen, such as, a bacterial cell wall component, and a pharmaceutically acceptable carrier, to a vertebrate subject by subcutaneous, intramuscular, or transdermal (i.e., transcutaneous) route, as expressly taught by Domenighini *et al.* (see column 8, lines 55-60), one would accomplish the method of "immunizing" the vertebrate host. Domenighini *et al.* explicitly teach such a method. That certain bacterial products, natural or mutated, inherently and necessarily serve as adjuvants and antigens is well known in the art. For instance, part (a) of claim 19 requires that LT-K63 be an "adjuvant", and LT-K63 detoxified mutant has been established in the art as a known "adjuvant" as evidenced by the teachings of Tommaso *et al.* or Partidos *et al.* (both of record). In addition, Clements *et al.* (WO 9606627 - Applicants' IDS) provide the general disclosure that mutant non-toxic LT serves as an immunogen by inducing anti-LT antibodies that cross-react with LT and cholera toxin (CT) and also as an adjuvant which can be administered by "parenteral" mode (see claims; page 20, lines 15-18; and page 17, lines 30-33). Claim 19 requires that LT-K63 be administered parenterally along with a pharmaceutically acceptable carrier and at least one selected antigen to a vertebrate subject in order to 'immunize' the subject. Domenighini *et al.* expressly disclose a method of vaccinating, i.e., immunizing an individual, by parenterally administering an immunologically effective amount of a composition comprising LT-K63 mutant. Domenighini's mutant composition comprises a pharmaceutically acceptable vehicle or carrier, such as, a protein, polysaccharide, polymeric amino acids and inactive virus particles, or bacterial cell wall components (see claims 4 and 1; column 8, lines 38-57; column 7, last two paragraphs; and paragraphs 1, 2 and 14). That proteins, polysaccharides and inactive virus particles serve as antigens is well known to those skilled in the art and is inherent from the disclosure of Domenighini *et al.* That bacterial cell wall components taught by the prior art qualify as a product containing 'at least one selected antigen' and therefore necessarily serve as effective antigens is inherent from the teachings of Domenighini *et al.* in light of what is well known in the art. For instance, Siadak *et al.* (US 4,834,975) and Golding (US 5,824,310) teach bacterial cell walls to be immunogenic and being capable of producing anti-LPS antibodies (see the last two paragraphs in column 2 of Siadak *et al.* and lines 13-18 in column 1 of Golding). Thus, Domenighini *et al.* teach the claimed methods and every elements in the instant claims.

Applicants' further state that the pending claims do 'specify' that their methods employ LT mutants as parenteral adjuvants. Applicants' allege that the Office has improperly applied the Domenighini reference in imposing a rejection of claims drawn to "methods directed to enhancing the immunogenicity of a selected antigen by using LT mutants as parenteral adjuvants". Applicants contend that "Domenighini also fails to describe and demonstrate another aspect of the pending claims -- methods of enhancing the immunogenicity of the selected antigen by co-administering LT mutant adjuvants". It should be noted that instant claims are **not** directed to *a method of enhancing the immunogenicity of a selected antigen* by co-administering *LT mutant adjuvants*, but rather to *a method of immunizing a vertebrate subject using a selected antigen* and a specific LT mutant [Emphasis added]. Only one of the recited adjuvant LT mutant species is administered; more than one LT mutant "adjuvants" are not co-administered in the claimed method. The features upon which Applicants rely are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)*.

It is noted that Applicants have not addressed the references of Tommasso *et al.* and Paradiso *et al.*

10) The rejection of claims 28-30 made in paragraph 15 of the Office Action mailed 01/12/01 (paper no. 19) under 35 U.S.C. § 103(a) as being unpatentable over Domenighini *et al.* (US 6,149,919) as applied to claim 19 and further in view of Rappuoli *et al.* (WO 95/17211, published 06/29/95 - Applicants' IDS) (WO '211), is maintained for reasons set forth therein and herebelow.

With regard to the teachings of Domenighini *et al.*, Applicants submit the same arguments that are described above. Applicants further state that claims 28-30 include methods of 'enhancing the antigenicity of a selected antigen using LT mutants as parenteral adjuvants' and that Domenighini does not teach or suggest that LT mutants can function as parenteral adjuvants for a selected antigen. With regard to Rappuoli *et al.*, Applicants contend that this reference does not teach LT mutants as parenteral mutants.

Applicants' arguments have been carefully considered, but are not persuasive.

Applicants' arguments with regard to the teachings of Domenighini *et al.* are addressed above. Claims 28-30 are not drawn to a method of enhancing the antigenicity of a selected antigen using the recited LT mutants. Instead, these claims are directed to a method of immunizing a vertebrate subject by administering an immunologically effective amount of one of the recited LT mutants and a selected antigen administered as recited. Applicants' arguments thus are not commensurate in scope with the invention claimed in the instant claims. The reference of Rappuoli *et al.* was applied to document that administration of an LT mutant along with an antigen simultaneously, sequentially or separately is well known in the art.

Applicants submit an abstract of a post-filing publication, McCluskie *et al.* (*Vaccine* 21: 2657-2660, 2001), which allegedly shows that the adjuvant effect of a molecule can be quite different when administered parenterally as compared to mucosally. It is noted that instant claims do not recite any generic 'molecule', but recite specific LT mutants in a generic manner as "adjuvants". McCluskie *et al.* teach of oligodeoxynucleotides as adjuvants, which teaching unrelated to LT mutants used in the instantly claimed method.

Applicants allege that the Office has not established a *prima facie* case of obviousness. As clearly set forth in paragraph 15 of the Office Action mailed 01/12/01 (paper no. 19), Domenighini *et al.* and Rappuoli *et al.* are **not** applied as anticipatory references in a 35 U.S.C. § 102 rejection, but in a 35 U.S.C. § 103 rejection. Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the claimed method of "immunizing" by administering an art-known adjuvant along with an antigen to a vertebrate subject is obvious over that of Domenighini *et al.* as modified by Rappuoli *et al.* given the knowledge in the art. Since non-toxic LT mutant adjuvants have already been used in the art by parenteral route (see also for example, Clements *et al.* WO 9606627) in methods of immunization as taught by Domenighini *et al.*, the instant claims are *prima facie* obvious over the combined teachings of Domenighini *et al.* and Rappuoli *et al.*

Remarks

11) Claims 19, 21, 23 and 25-27 stand rejected. Claim 24 stands objected to.

12) The Applicants' amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

14) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. DEVI, PH.D.
PRIMARY EXAMINER

October 2001